

RESEARCH ARTICLE

Trends in breast cancer in the elderly in Denmark, 1980–2012

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ABSTRACT

Background Breast cancer is the most frequent malignancy among women worldwide and the second most common cause of cancer-related death in developed countries. The aim of the present analysis is to describe trends in incidence, mortality, prevalence, and relative survival in Denmark from 1980 to 2012 focusing on age, comparing persons aged 70 years or more with those aged less than 70 years.

Material and methods Cancer of the breast was defined as ICD-10 code C50. Data derived from the NORDCAN database with comparable data on cancer incidence, mortality, prevalence and relative survival in the Nordic countries, where the Danish data were delivered from the Danish Cancer Registry and the Danish Cause of Death Registry with follow-up for death or emigration until the end of 2013.

Results The proportion of patients diagnosed with breast cancer over the age of 70 years increased with time to 29% of women and 44% of men in 2012. Incidence rates increased with time and peaked around 2010 in all age groups except for those aged 90 years or more. Mortality rates were clearly separated by age with increasing mortality rates by increasing age group for both women and men. Relative survival increased over time in all age groups, but patients aged 70 years or more had a poorer relative survival than those aged less than 70 years. In 2012, 58 521 persons (all ages) were alive in Denmark after a diagnosis of breast cancer.

Conclusion Poorer survival of Danish breast cancer patients over the age of 70 years is likely to be due to inferior treatment and non-adherence to treatment guidelines. There is a need for clinical trials focusing on patients over the age of 70 years.

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Breast cancer is the most frequent malignancy among women worldwide and the second most common cause of cancer-related death (after lung cancer) in developed countries [1]. In Denmark, the incidence has been increasing steadily since the 1960s and the mortality has declined resulting in an improvement in survival [2]. The improved prognosis is assumed to be the result of earlier diagnosis, particularly the use of mammography screening, and improved treatment, especially the use of more effective adjuvant therapy [3].

Gender is the strongest risk factor for developing breast cancer with a male:female ratio of approximately 1:100 [1]. The rarity of breast cancer in men has made it difficult to study etiologic factors. Recently, the Male Breast Cancer Pooling Project published results from 11 case-control and 10 cohort studies, including a total of 2405 male breast cancer cases and 52 013 controls without breast cancer, including 156 cases and 468 controls from the Nordic countries [4]. The risk of men developing breast cancer increased with increasing recent BMI, a family history of breast cancer, Klinefelter syndrome, and medical conditions like diabetes mellitus, cryptorchidism, and a history of fractures [4].

Age has a pronounced effect on the risk of developing breast cancer both in men and in women with increasing incidence rates with increasing age. The peculiar shape of the age-specific incidence curve with a “hook” or change in slope around age 50 in women was first described by Johannes Clemmesen, founder of the Danish cancer registry, in 1948 [5]. It has been associated with a protective effect of menopause in women and lead to the hypothesis that risk factors may differ in pre- and postmenopausal women. In men, the age-specific incidence curve is a straight line of a constant increase with age [6].

Apart from gender and age, the risk of developing breast cancer is increased in persons carrying mutations in the BRCA1 and BRCA2 genes. In women, reproductive factors, such as parity and late age at first birth, are associated with a higher risk in premenopausal than in postmenopausal women while risk estimates for increasing alcohol intake and BMI are higher for postmenopausal women [7].

The aim of the present analysis is to describe trends in incidence, mortality, prevalence, and relative survival in Denmark from 1980 to 2012 focusing on age, comparing

Table II. Average annual number of deaths from breast cancer in Denmark, 1980–2012.

	0–69 year			70–74 year			75–79 year			80–84 year			85–89 year			90+ year			All ages									
	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)	Cases male (mortality)		Cases female (mortality)							
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%						
1980	3	41.7	607	54.4	1	8.3	155	13.9	3	36.1	134	12.0	0	5.6	112	10.0	0	5.6	73	6.6	0	2.8	34	3.1	7	100	1116	100
1990	5	55.6	689	51.8	1	6.7	166	12.5	1	13.3	166	12.5	1	13.3	146	11.0	1	6.7	106	8.0	0	4.4	58	4.3	9	100	1329	100
2000	4	37.5	659	48.8	2	20.8	154	11.4	1	14.6	156	11.6	1	8.3	137	10.1	1	6.3	88	6.5	10	6.3	88	6.5	10	100	1350	100
2005	4	33.3	578	46.4	2	16.7	149	11.9	2	16.7	149	11.9	2	13.6	149	12.0	2	12.1	125	10.0	1	7.6	97	7.8	13	100	1246	100
2010	3	60.0	557	45.9	0	0.0	144	11.9	0	0.0	129	10.6	0	0.0	148	12.2	1	20.0	139	11.4	1	20.0	97	8.0	5	100	1214	100
2011	4	50.0	526	43.3	0	0.0	128	10.5	1	12.5	148	12.2	1	12.5	168	13.8	0	0.0	137	11.3	2	25.0	108	8.9	8	100	1215	100
2012	2	22.2	505	45.0	0	0.0	135	12.0	2	22.2	136	12.1	1	11.1	131	11.7	3	33.3	122	10.9	1	11.1	94	8.4	9	100	1123	100

Adjusting for changes in population size and age, Figure 1 illustrates that no clear pattern in incidence rates were seen with age among men, probably due to the small number of patients. In women, the incidence rates increased with time and peaked around 2010 in all age groups except for those aged 90 years or more. The incidence increased with age, the rates among women aged 70 years or more being about three times higher than among those aged less than 70 years. The mortality rates (Figure 2) were clearly separated by age groups with increasing mortality rates by increasing age group for both women and men. There was no evident trend with time in the mortality rates.

Prevalence

Since 1980 the prevalence of breast cancer has been increasing substantially (Table III). In 2012, 58 521 persons (all ages) were alive in Denmark after a diagnosis of breast cancer, 264 men and 58 257 women. The proportion of persons aged 70 years or more has also increased to 43% (25 361 of 58 521) in 2012.

Survival

Age-specific relative survival is shown in Figure 3 for women only, as there were too few men to provide stable estimates. Both the one- and the five-year relative survival increased steadily over time for all age groups. Thus, for patients (0–69 years) diagnosed from 1968 to 1972, the five-year relative survival increased from 62% (95% CI 61–63%) to 90% (95% CI 89–90%) for those diagnosed from 2008 to 2012. Correspondingly, for patients (70–79 years) diagnosed from 1968 to 1972, the five-year relative survival increased from 55% (95% CI 52–58%) to 80% (95% CI 79–81%) for those diagnosed from 2008 to 2012.

With respect to age, both the one- and five-year relative survival decreased with increasing age group but the differences diminished with time. Thus, in the most recent period from 2008 to 2012, the relative five-year survival was similar for women aged 80–89 years (73%, 95% CI 70–75%) and women aged 90 years or more (75%, 95% CI 64–86%).

Discussion

Age has a pronounced influence on incidence and mortality from breast cancer in men and women with increasing rates with increasing age. The rarity of breast cancer in men precluded an analysis of survival but evidence from 1429 male breast cancer patients from the Nordic countries has shown that the relative survival was three-fold higher among men aged 80 years or more compared with those aged 40 years or less [10]. It was concluded that important differences exist between male and female patients in the association between survival and age at diagnosis, possibly related to a later stage at diagnosis in men.

In women, the incidence of breast cancer increased from 1980 to 2010 and then declined while no clear trends were seen in the mortality rates, resulting in increasing survival over time. The peak in incidence just before 2010 among women aged less than 70 years can be explained from introduction of

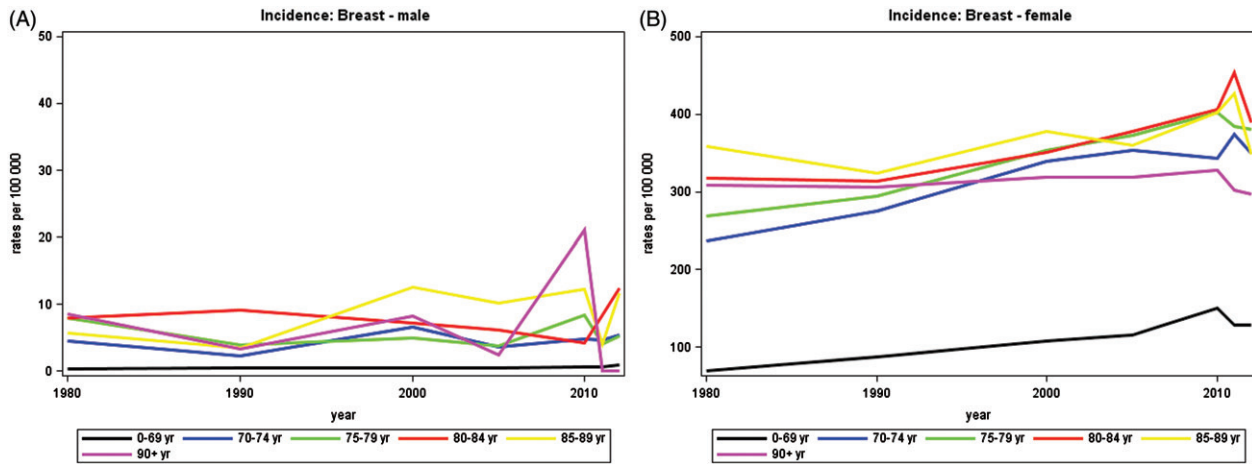


Figure 1. Incidence rates of breast cancer in Denmark, 1980–2012, by age group. A. Males, B. Females.

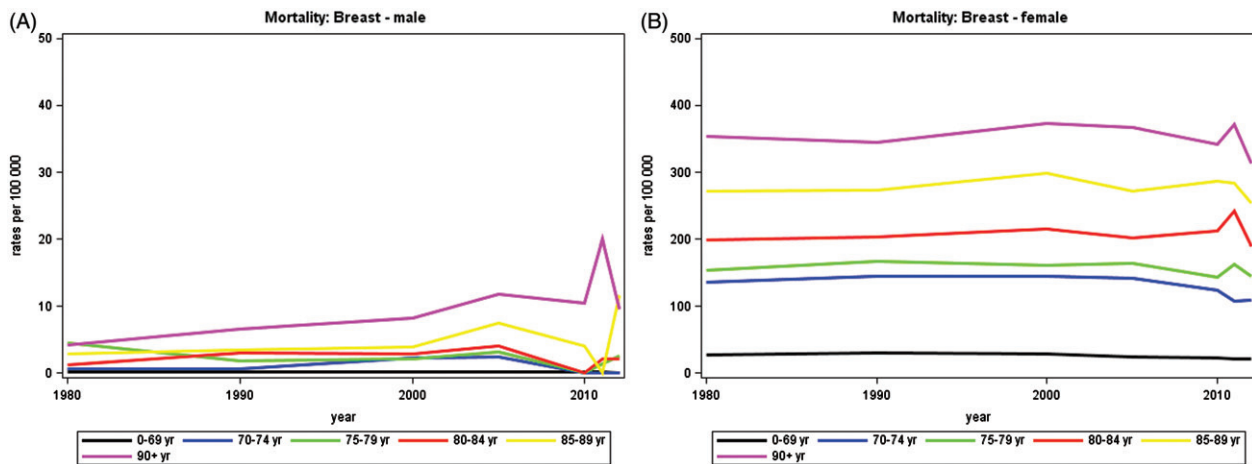


Figure 2. Mortality rates from breast cancer in Denmark, 1980–2012, by age group. A. Males, B. Females.

mammography screening. The first mammography screening program started in 1991 but covered only about 20% of Danish women aged 50–69 years. The national roll-out of mammography screening took place from 2008 to 2010 in Denmark [11]. An equivalent peak in incidence was not observed for women aged of 70 years or more.

With the increasing incidence and the almost constant mortality, survival after breast cancer has increased over time for all age groups. However, when the mortality from other causes than breast cancer has been taken into account in the relative survival, women aged 70 years or more still have a poorer survival than those less than 70 years. These results are consistent with other studies [12,13]. As breast cancers among elderly women are associated with a more favorable tumor biology, more often being hormone receptor positive and human epidermal growth factor receptor-2 negative compared with younger women, the poorer survival is likely to be due to an inferior treatment. This has been documented in several studies, showing that women aged over 74 years were more likely to receive no treatment, surgery alone, or hormone therapy alone compared with younger patients, and that elderly patients were undertreated according to national guidelines [14]. In Denmark, the national guidelines for

adjuvant breast cancer treatment did not include patients over 75 years until 2002, and the guidelines for adjuvant radiotherapy still recommend an individual assessment of expected benefit versus harm among patients aged over 75 years.

There are several reasons why treatment guidelines do not include elderly patients. Guidelines are mostly based on evidence from randomized clinical trials and elderly patients with early breast cancer are underrepresented in such adjuvant trials [15–17], e.g. the Early Breast Cancer Trialists' Collaborative Group overview [17] included only 651 patients aged 70 years or more of a total of 44 251 patients randomized to polychemotherapy with anthracyclines versus taxanes, i.e. 1.5%. The estimates of benefit from polychemotherapy among patients aged 70 years or more were similar or even greater than in younger patients, but less precise, i.e. not significant, probably because of the smaller number of patients. Second, randomized clinical trials often exclude patients with comorbidity and the incidence of comorbidities increases with age [18]. In Denmark, comorbidity is present in approximately 26% of breast cancer patients [19], and has a significant and independent impact on survival after early-stage breast cancer, with poorer survival among patients with

Table III. Annual number of persons alive with breast cancer in Denmark by December 31, 1980–2012.

	0–69 year				70–74 year				75–79 year				80–84 year				85–89 year				90+ year				All ages			
	Prev cases male		Prev cases female		Prev cases male		Prev cases female		Prev cases male		Prev cases female		Prev cases male		Prev cases female		Prev cases male		Prev cases female		Prev cases male		Prev cases female		Prev cases male		Prev cases female	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1980	46	41.8	11847	60.4	18	16.4	2771	14.1	20	18.2	2296	11.7	17	15.5	1568	8.0	7	6.4	835	4.3	2	1.8	284	1.4	110	100	19601	100
1990	54	41.5	15518	58.0	16	12.3	3444	12.9	25	19.2	3259	12.2	22	16.9	2510	9.4	11	8.5	1427	5.3	2	1.5	581	2.2	130	100	26739	100
2000	69	39.9	21432	58.0	27	15.6	4576	12.4	25	14.5	4475	12.1	27	15.6	3294	8.9	22	12.7	2099	5.7	3	1.7	1057	2.9	173	100	36933	100
2005	92	45.3	25760	58.5	29	14.3	5471	12.4	29	14.3	4850	11.0	27	13.3	4088	9.3	17	8.4	2522	5.7	9	4.4	1365	3.1	203	100	44056	100
2010	106	46.3	31928	58.5	29	12.7	7428	13.6	39	17.0	5771	10.6	22	9.6	4562	8.4	20	8.7	3144	5.8	13	5.7	1772	3.2	229	100	54605	100
2011	105	44.1	32566	57.7	38	16.0	7969	14.1	43	18.1	6162	10.9	23	9.7	4609	8.2	15	6.3	3206	5.7	14	5.9	1919	3.4	238	100	56431	100
2012	118	44.7	33042	56.7	47	17.8	8576	14.7	42	15.9	6518	11.2	28	10.6	4768	8.2	20	7.6	3323	5.7	9	3.4	2030	3.5	264	100	58257	100

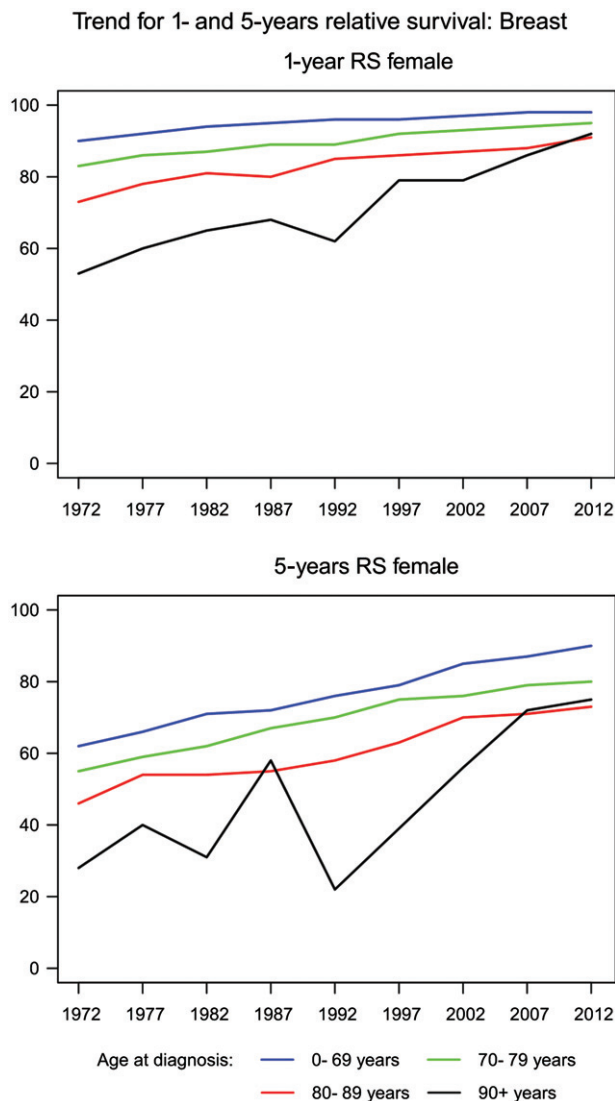


Figure 3. Age-specific relative survival after breast cancer in Denmark.

one or more comorbid conditions [19–21]. However, patients with mild to moderate comorbidity (Charlson Comorbidity Index of 1 and 2) receiving chemotherapy had similar breast cancer mortality as patients with no comorbidity [20]. This indicates that the effects of chemotherapy in the elderly with mild/moderate comorbidity are similar to the benefits among patients with no comorbidity.

There is a substantial variation in breast cancer treatment by age, probably because of lack of knowledge about treatment effects in the elderly [22]. Data collected from elderly women not treated in clinical trials show that clinician preferences influence the choice of adjuvant chemotherapy for elderly patients [23].

The average life expectancy for a Danish woman born today is 82 years [24]. The decision about breast cancer therapy in elderly patients should take into account life expectancy, comorbidity, risk of breast cancer recurrence (i.e. disease stage and tumor characteristics), and functional status. Today, age alone should not be an appropriate criterion for treatment decisions. If at all possible, patients should be offered guideline therapy but it is necessary to monitor closely the toxicity as the elderly are frailer than younger patients [25].

There is still a need of conducting trials evaluating the efficacy of less intense treatment among elderly breast cancer patients since incidence rates are high in this age group. Age over 70 years and co-existing comorbidities should be allowed in such trials to reflect the target population.

Conclusion

Danish breast cancer patients over the age of 70 years have a poorer prognosis with increased mortality rates and poorer relative survival compared to the younger patients. This is likely to be due to inferior or non-guideline therapy of the elderly patients. With the increasing longevity of breast cancer patients, more clinical trials are needed with particular focus on the elderly population.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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